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(21) International Application Number: PCT/US94/09466 (22) International Filing Date: 26 August 1994 (26.08.94) (30) Priority Data: 08/112,330 27 August 1993 (27.08.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/112,330 (CIP) Filed on 27 August 1993 (27.08.93) (71) Applicant (for all designated States except US): NOVEN PHARMACEUTICALS, INC. [US/US]; 13300 S.W. 128th Street, Miami, FL 33186 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MANTELLE, Juan, A. [US/US]; 10821 Southwest 92nd Avenue, Miami, FL 33176 (US). GOLUB, Allyn, L. [US/US]; Suite 300, 18441 Northwest 2nd Avenue, Miami, FL 33169 (US). (74) Agents: MELOY, Sybil et al.; Foley & Lardner, Suite 500, 3000 K Street, N.W., Washington, DC 20007-5109 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: COMPOSITIONS AND METHODS FOR THE ADMINISTRATION OF δ -AMINOLEVULINIC ACID (57) Abstract A pharmaceutical composition of increased stability, which comprises ALA and a pharmaceutically acceptable, flexible, finite carrier suitable for administration to the skin or other dermal membrane of a mammal, optionally containing a stabilizing amount of an organic weak proton donor or saccharide containing substance. The pharmaceutically acceptable carrier in solid formulation can be a skin patch, many forms and types of which are known and used in the art. It is preferable that the composition be anhydrous. The formulations appear to improve the fluorescence produced after exposing treated skin to activating light, as compared with the fluorescence produced with ALA in a fluid carrier. In particular, the pattern of fluorescence is more even and uniform over the area of application than with topical creams or salves and may provide increased fluorescence.		

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COMPOSITIONS AND METHODS FOR THE ADMINISTRATION OF
 δ -AMINOLEVULINIC ACIDCross-Reference to Related Applications

5 This application is a continuation-in-part of Serial
No. 08/112,330 filed August 27, 1993, which is a
continuation-in-part of PCT/US92/01730, filed February
27, 1992, which is a continuation-in-part of U.S.
Application Serial No. 07/813,196, filed December 23,
10 1991, now U.S. Patent No. 5,234,957, which is a
continuation-in-part of U.S. Patent Application Serial
No. 07/661,827, filed February 27, 1991 and now
abandoned. All of the foregoing applications are hereby
incorporated by reference.

15 Background of the Invention

5-Aminolevulinic acid, also referred to as δ -
aminolevulinic acid or 5-amino-4-oxopentanoic acid, is
referred to herein as "ALA". ALA has been known for over
40 years to be a precursor in the metabolic pathway to
20 heme in humans and to chlorophyll in plants. Until the
past ten years ALA has been of limited usefulness,
namely, use limited to porphyrin research. In 1984, ALA
was proposed for use as a photodynamic herbicide. It has
been discovered recently that ALA can be used by various
25 routes of administration to detect and treat certain
conditions involving rapidly metabolizing cells, namely
hyperproliferative cells. It is especially useful in the
treatment of malignant and non-malignant abnormal
growths.

30 ALA has been administered by various routes known for
use in drug administration, but especially by topical
application to the skin and epithelium of various body
cavities. Application of ALA results in the selective

accumulation of clinically significant amounts of protoporphyrin IX, another precursor in the metabolic pathway to heme. Activation of protoporphyrin IX by light, depending on the wavelength of the light, will
5 cause the protoporphyrin IX either to fluoresce (which can be used as the basis of a detection method), or to decompose (which can be used as the basis of treatment for cells that need to be removed).

ALA previously has been used in clinical testing on
10 humans and other mammals in aqueous and non-aqueous fluid vehicles such as creams (oil in water emulsions) and lotions for application to the skin and orally for the diagnosis and treatment of skin cancers. ALA has been used in clinical studies in aqueous solution for
15 application to the endometrial cavity.

ALA has been reported to inhibit degradation of the drug calcitonin by the nasal mucosa peptides in U.S. 5,026,825 . Preparations in the examples of that patent show a combination of calcitonin and ALA in
20 aqueous solutions containing one or more of benzalkonium chloride, citric acid, sodium citrate, hydrochloric acid, sodium acetate and acetic acid. The organic acids and their salts appear to be used as buffers, to adjust the pH of the resulting solution to about 4.

25 ALA has a tendency to decompose in a wide variety of vehicles used in clinical testing including both water containing vehicles, anhydrous fluid vehicles and water and oil emulsions. In general, the higher the pH of the fluid vehicle, the more rapid the degradation. For
30 example, addition of about 10% by weight ALA in the form the hydrochloride salt into an alkaline solution, left at room temperature, results in almost complete degradation in about one week.

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The decomposition occurring with fluid preparations, such as water and ethanol, reported in the scientific literature with use of ALA patients, is sufficient to preclude the use of ALA in a product to be distributed in normal, existing channels for the supply of pharmaceuticals. Many studies have been performed without success in an attempt to stabilize ALA, with respect to extending the stability of the chemical in a fluid, including use of an aqueous solution containing certain antioxidants such as ascorbic acid and sodium bisulfite. Thus, there remains a need for a storage stable composition comprising ALA in a form suitable for administration to a patient.

Summary of the Invention

The invention relates to a pharmaceutical composition of increased stability, which comprises ALA and a pharmaceutically acceptable, flexible, finite carrier suitable for administration to the skin or other dermal membrane of a mammal, optionally containing a stabilizing amount of an organic weak proton donor or a saccharide.

The pharmaceutically acceptable carrier in solid formulation for topical delivery to the skin is desirably a skin patch, many forms and types of which are known and used in the art. It is preferable that the composition be prepared without - and essentially contain no - water. Not only are these formulations using a topical solid carrier stable after prolonged storage, but use of the formulations appear to improve the fluorescence produced after exposing treated skin to activating light, as compared with the fluorescence produced with ALA in a fluid carrier. In particular, the pattern of fluorescence is more even and uniform over the area of application than with topical creams or salves and may even provide increased fluorescence.

When preparing the solid formulations for topical administration, addition of a proton donor, such as a weak organic acid, can be used to increase the long-term stability of the patch. Suitable organic acids are mono- and polycarboxylic acids such as citric acid, oxalic and ascorbic acids. Weak organic acids are preferred because they are less irritating and less likely to affect the stability of the ALA. The additive also can be a saccharide. If the solid preparation contains water, it is essential to include the stabilizing amount of a proton donor or saccharide-containing substance. Anhydrous preparations, however, are preferred.

The term "stabilizing amount," when applied to the mild organic proton donor or the saccharide-containing substance of the present invention, means a concentration sufficient to prevent or minimize the degradation of ALA over the expected storage time for the composition, typically 6 months to two years. In general, this amount should be an amount at least equal in weight to the ALA present, although concentrations as high as four times the weight of ALA can be used. The saccharide-containing substance can be a complex saccharide such as starch, a gum or a polysaccharide or it can be less complex saccharide such as a monosaccharide.

The mechanism by which the solid topical formulation stabilizes the ALA is unknown. The mechanism by which the weak organic proton donor such as the weak organic acid or the saccharide-containing substance increases the stability of ALA also is unknown. It cannot be explained merely as a reducing effect which prevents the oxidation of ALA, since other anti-oxidants, such as Vitamin E, BHT, BHA, ascorbic acid and sodium bisulfite used in an aqueous solution, were not found to be effective at increasing the stability of ALA. It is unknown whether this effect is one of protection by the saccharide-containing substance of the degradation sites on the ALA.

This invention also comprises the method of stabilizing ALA by mixing the same with an anhydrous, flexible, finite, pharmaceutically acceptable carrier for topical administration. The carrier also may comprise a weak organic proton donor or saccharide, a solid polymer, or two or more of the foregoing.

Detailed Description of the Preferred Embodiments

It now has been found that ALA can be prepared in a stable formulation for topical use by incorporation into a topical drug delivery carrier, optionally containing a mild organic proton donor or saccharide containing substance. In a preferred embodiment, the delivery carrier is contained in a patch. Use of topically acting ALA in a patch is unusual since, because of the increased costs associated with manufacture of patches. Typically, because of these costs, patches are used only for prescription drugs intended for systemic effect, but which are given topically to avoid degradation by the liver or to prolong the rate and extent of distribution.

ALA, in addition to the meaning given above, is used throughout this application to refer to pharmaceutically acceptable salts of ALA, which are considered equivalent for purposes of this invention. The nature of such salts are known to skilled workers in the arts. Such pharmaceutically acceptable salts include, but are not limited to, acid addition salts with inorganic and organic acids as well as quaternary ammonium salts of ALA. Suitable inorganic salts include hydrochloride, hydrobromide, sulfate, carbonate, hydrogen carbonate, hydrogen sulfate and like inorganic salts known for use with pharmacologically active substances. Suitable organic acids are those mono- and polycarboxylic acids such as citric acid, ascorbic acid, oxalic acid and benzoic acid which are weak acids and can also act as a proton donor. A suitable quaternary ammonium salt is

olealkonium chloride and other quaternary ammonium salts that are generally recognized as safe and effective ("GRAS") under the food and drug laws for application to dermal membranes.

5 The stability of ALA may be increased by incorporating it into a solid, pharmaceutically acceptable carrier, preferably a topical carrier and more preferably in an anhydrous adhesive topical carrier. The solid carrier can optionally contain an organic weak
10 proton donor such as a weak organic acid, or a saccharide-containing substance.

 The term "pharmaceutically acceptable carrier" used here with reference to topical administration refers to the wide variety of carriers known for use for
15 application to the skin or body cavity to a dermal membrane. Such carriers are well known in the art.

 The term "organic weak proton donor" used here refers to an organic substance known to function as a weak acid which does not, at the same time, degrade the ALA.
20 Whether the organic substance will degrade the ALA can be determined easily by placing the substance at the concentration intended for use with the ALA, then analyzing for residual ALA. Suitable organic weak proton donors are organic weak acids such as mono- and
25 polycarboxylic acids such as citric acid, oxalic acid, ascorbic acid and benzoic acid. Other suitable stabilizers are gums such as guar gum, xanthan gum, karaya gum, British gum, starch gum, tragacanth gum, pectin gum and derivatives thereof, saccharides such as
30 complex saccharides such as cellulose, polysaccharides such as dextran and dextrin, and monosaccharides such as dextrose, fructose, maltose, D-glucose and L-glucose. Corn syrup, composed of dextrin and glucose is particularly useful, but its use is limited by the fact
35 that it generally contains water.

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The solid topical forms of the present invention include all the known types of devices, including both the adhesive matrix and reservoir devices. Matrix devices are preferred because the minimization of the number of layers of the device results in ease of preparation. The matrix devices are prepared by methods known in the art. The most convenient form for manufacture of a matrix device is one in which the ALA is dispersed in a pressure sensitive adhesive. The matrix devices are preferably prepared using commercially supplied organic solvents containing the polymer. The additional ingredients are added to the mixture and then the solvents are removed to form the patch. This avoids the use of or inclusion of water in the composition and the need to perform a cross-linking step after the mixing, such as is necessary for emulsion polymerization.

Pressure sensitive adhesives useful in preparing the preferred topical compositions include a wide variety of polymeric adhesives including pharmaceutically acceptable acrylics, vinyl acetate, silicone and synthetic or natural rubber adhesives and mixtures thereof. Acrylic adhesives include Gelva adhesives GMS 1430, 788 available from Monsanto Co. and various Durotak adhesives such as 87-2852 manufactured by National Starch. Vinylacetate adhesives including Flexbond 149 and 150 from Air Products are of limited usefulness because they contain water. Rubber based adhesives such as the Morstiks from Morton Thiokol, Ins. or Vistanex manufactured by Exxon Chemicals can be used. Numerous silicone based adhesives are available from Dow-Corning. These and other pressure sensitive adhesives suitable for topical application will be apparent to one skilled in the art.

For adhesive matrix devices, the polymer blend is applied to a suitable backing material impermeable to the drug or the other components of the polymer matrix. The backing materials, which are preferably water resistant,

and occlusive or non-occlusive, can be selected from such material as foam, metal foil, polyester, low density polyethylene, copolymers of vinyl chloride and polyvinylidene chloride and laminates thereof.

5 Where the topical device is a reservoir-type device, the ALA in a solvent, preferably in a non-aqueous solvent such as an alkanediol or an organic acid such as citric acid is used to fill the reservoir. About 0.1 to about 2%, preferably about 0.5% of a gelling agent such as
10 hydroxypropyl cellulose, can be added to form a gel. The solution or gel is retained in the reservoir by a suitable rate-controlling membrane such as an ethylene-vinyl acetate copolymer membrane, which membrane preferably has a face layer of a pressure sensitive
15 adhesive as described above. Backing materials are similar to those described above for matrix devices.

Both adhesive matrix and reservoir devices contain a release liner impermeable to the drug and any solvents present in the system in order to protect the adhesive
20 layer until the patch is to be applied to the skin. Typical materials for release liners are polyester, polyethylene, and polyethylene coated paper, preferably silicon-coated to facilitate removal.

The adhesive matrices of the present invention
25 contain 0.5 to 50% ALA, preferably 5 to 20% and more preferably 10 to 20%, 50 to 95% adhesive, preferably 60 to 90% and more preferably 70 to 90%, and optionally, 0 to 40% carrier for the ALA and penetration enhancer. Since the ALA in the solid formulation is used for a
30 topical effect, there is in fact no maximum limitation as to the amount of ALA that can be used in the patch except to the extent that the adhesiveness or stability of the patch is affected.

Methods for preparing adhesive matrix devices are known in the art. A preferred method for preparing adhesive matrix topical devices of the present invention comprises coating a thin layer of the adhesive polymer containing the ALA optionally in an anhydrous solvent and optionally containing a mild organic proton donor such as saccharide-containing substance or a mild organic acid onto the material to be used as a release liner, cross-linking the polymer blend in the case of an adhesive to be cross-linked, drying the release liner containing the polymer mixture, then laminating the backing material to the resultant adhesive layer. The preferred proton donor for the ALA is any liquid material or a saccharide-containing substance or an organic acid such as citric acid in a non-aqueous solvent. Additional substances which increase the passage of the drug into the skin also can be added. Suitable sized patches can then be cut out and the patches preferably sealed in protective pouches.

The layer of polymer mixture cast on the release liner according to the preferred method of this invention is about 5 mils to about 30 mils thick. The coated layer is preferably dried at a temperature of about 80 degrees Centigrade.

The size of the topical device of the present invention depends on the dose of ALA to be utilized, with the preferred patch area being about 2.5 to 20 cm², preferably 5 to 15 cm². The preferred delivery rate for ALA is at least 0.1 µg. per cm² per hour, giving a preferred daily dosage of at least 0.25 mg. per day applied to the area of the skin to be diagnosed or treated for about 2-48 hours. The optimum concentration of ALA in a patch is at least 0.1-3.0 mg. per cm².

As a minimum, the topical device must contain a pharmacologically effective amount of ALA. Generally, this is at least 0.25 mg. The duration of application is

that period sufficient to achieve ALA penetration into the diseased tissue and that permits high localized concentrations of protoporphyrin IX resulting from the conversion of ALA. This period may be about 3-24 hours and, preferably, is 12-16 hours. The effective amount and duration will vary depending on the nature of the lesion and may be determined empirically by those skilled in the art by testing localized fluorescence of the lesion after administration. If fluorescence is insufficient, longer application or higher ALA concentrations may be used.

Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light. A suitable wavelength is 400 nm, 634 nm or 600-700 nm, at an intensity of 10-100 milliwatts per centimeter squared (mW/cm²) to provide a light dose of 10-100 Joules/cm². Exposure time may vary from 3 to 30 minutes, but preferably is about 10 minutes. Upon exposure, activation of protoporphyrin IX leads to *in situ* breakdown of protoporphyrin IX and the generation of singlet oxygen, leading to the destruction of diseased cells.

The target tissues for which the present invention may be used are any visible, cutaneous lesion or other undesired rapidly growing cells. In particular, these include, but are not limited to, neoplastic, aplastic and hyperplastic skin conditions such as basal cell carcinoma, actinic keratosis, psoriasis and similar conditions.

Example 1

The following table shows typical adhesive matrix formulations of this invention. In this table GMS means Gelva multipolymer system, and the percentages shown are percentages by weight:

Gelva Multipolymer Solution = Acrylic Adhesive = GMS

	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
GMS 1430	80	90	80	70	65	80		
ALA	10	10	10	10	10	10		
Citric Acid	10	—	5	10	5	—		
Corn Syrup	—	—	5	10	20	10		
GMS 788	80	90	80	70	60	50	50	
ALA	10	10	10	10	10	10	10	
Citric Acid	10	—	5	10	—	—	10	
Corn Syrup	—	—	5	10	30	40	30	
GMS 788	40	80	70	35	30	25	25	45
GMS 1430	40	5	5	35	30	25	25	45
ALA	10	10	10	10	10	10	10	10
Citric Acid	10	5	5	10	—	—	10	—
Corn Syrup	—	—	10	10	30	40	30	—
Duro-Tak 87-2852	80	80	50	50	60	70	70	90
ALA	10	10	10	10	10	10	10	10
Citric Acid	10	—	—	10	10	5	—	—
Corn Syrup	—	10	40	30	20	15	20	—

Example 2

In the following example the ALA, propylene glycol, lecithin and glycerin are blended at about 70 to 90°C until all the drug is dissolved. The solution is then
 5 cooled to about 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven polyester film (for example, the film sold under the trademark Sontara 8100, manufactured by DuPont de
 10 Nemours, Wilmington, DE) and warmed to about 100°C to accelerate the formation of the gel into its final, finite form.

5-Aminolevulinic Acid

	%w/w	%w/w	%w/w	%w/w	%w/w
ALA	2	5	10	15	20
15 Solvent (dipropylene glycol)	10	10	15	15	15
Solvent (Oleic acid)	10	10	10	10	10
Solvent (glycerin)	30	30	20	20	30
Solvent (isocetyl alcohol)	—	—	10	10	—
Bioadhesive (karaya gum)	30	30	20	20	30
20 Bioadhesive (xantham gum)	—	—	10	10	—
Binder (lecithin)	18	15	10	10	—

Example 3

A thirty-two year old female is diagnosed with basal cell carcinoma. A single lesion is evident on her right forearm covering approximately 22 mm², and topical aminolevulinic acid photodynamic therapy (ALA PDT™) is prescribed.

A 5 cm² topical patch containing 10% (w/w) ALA, made according to Example 2, is applied to the lesion. The patch is left in place for 18 hours, which is sufficient to permit adequate penetration of ALA into the lesion and for the formation of protoporphyrin IX ("PpIX"), the active endproduct of topical ALA administration. After the patch is removed, the lesion is wiped with an alcohol swab to remove any residual adhesive.

The lesion is then exposed to activating UV light using a conventional Woods lamp to determine if the fluorescence levels, and hence the PpIX levels, are sufficient. Finding the levels suitable, the lesion is then exposed to a 634 nm wavelength light source at 100 mW/cm² for 15 minutes.

Within 30 minutes, a localized reaction is observed, characterized by the rapid onset of redness, erythema and edema at the treatment site. During the next several days, necrosis of the destroyed lesional cells ensues, resulting in the formation of a burn-like scab over the former lesion. During the next six weeks, normal healing of the treated tissue and restoration of intact skin is observed.

The foregoing examples are illustrative embodiments of the invention and are merely exemplary. A person skilled in the art may make variations and modification without departing from the spirit and scope of the

invention. All such modifications and variations are intended to be included within the scope of the invention as described in this specification and the appended claims.

What Is Claimed Is

1. A pharmaceutical composition comprising:
 - (i) a therapeutically effective amount of the drug δ -aminolevulinic acid; and
 - (ii) a pharmaceutically acceptable, flexible, finite carrier for dermal application.
2. The pharmaceutical composition of claim 1, wherein the drug is dispersed throughout the carrier.
3. The pharmaceutical composition of claim 2, wherein the carrier is an adhesive.
4. The pharmaceutical composition of claim 3, wherein the adhesive is a pressure-sensitive adhesive.
5. The pharmaceutical composition of claim 4, wherein the pressure sensitive adhesive is a bio-adhesive.
6. The pharmaceutical composition of claim 4, wherein the pressure sensitive adhesive is a synthetic adhesive selected from the group consisting of polyacrylates, polysiloxanes and polyisobutylenes, or mixtures thereof.
7. The pharmaceutical composition of claim 4, wherein the adhesive additionally contains a stabilizing amount of a saccharide.
8. The pharmaceutical composition of claim 7, wherein the saccharide is selected from the group consisting of dextrans, dextrans, polysaccharides, disaccharides and monosaccharides.
9. The pharmaceutical composition of claim 8, wherein the monosaccharide is selected from the group

consisting of dextrose, fructose, D-glucose and L-glucose.

10. The pharmaceutical composition of claim 8, wherein the saccharide is a mixture of a substance selected from the group consisting of dextrans, dextrans and monosaccharides.

11. The pharmaceutical composition of claim 4, wherein the adhesive additionally contains a stabilizing amount of an organic weak proton donor.

12. The pharmaceutical composition of claim 11, wherein the organic weak proton donor is a substituted or unsubstituted alkanolic acid.

13. The pharmaceutical composition of claim 12, wherein the alkanolic acid is selected from the group consisting of citric acid, oxalic acid, ascorbic acid and benzoic acid.

14. The pharmaceutical composition of claim 13, wherein said composition is substantially anhydrous.

15. The pharmaceutical composition of claim 13 comprising, in parts by weight, about 1 to about 30 parts δ -aminolevulinic acid, about 1 to about 30 parts of an organic weak acid and about 40 to about 98 parts of a polyacrylate adhesive.

16. The pharmaceutical composition of claim 10, wherein the dextran is of molecular weight of at least 70,000 daltons.

17. The pharmaceutical composition of claim 7, wherein the saccharide is present in a concentration of from about 10 to about 80% by weight.

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18. A method of stabilizing δ -aminolevulinic acid, comprising mixing the δ -aminolevulinic acid with an anhydrous, flexible, finite pharmaceutically acceptable carrier suitable for topical administration.

19. The method of claim 18, wherein a weak organic proton donor is also added to the mixture.

20. The method of claim 18, wherein said proton donor is selected from the group consisting of substituted or unsubstituted alkanolic acids.

21. The method of claim 18, wherein said carrier is an adhesive.

22. The method of claim 21, wherein said adhesive is a pressure sensitive adhesive.

23. The method of claim 22, wherein said adhesive is selected from the group consisting of bioadhesives and synthetic polymeric adhesives.

24. The method of claim 23, wherein said synthetic polymeric adhesive is selected from the group consisting of polyacrylates, polysiloxanes and polyisobutylenes, or mixtures thereof.

25. A method of administering δ -aminolevulinic acid which comprises applying a therapeutically effective amount of the δ -aminolevulinic acid in a flexible, finite carrier to a dermal membrane.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/09466

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195 A61K9/00 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 15289 (NOVEN PHARMACEUTICALS INC.) 17 September 1992 cited in the application see claims 1,4,9,10,14,26 ---	1,18,19
A	EP,A,0 358 234 (RORER INTERNATIONAL) 14 March 1990 cited in the application see claims 1,17-19 see page 2, line 1 - line 4 see page 11, line 34 - line 39 -----	1,18,19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

information on patent family members

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